FUND

WEEK 7
DRUGS & PHARMACOLOGY

THIS WEEK

- AT — Population Genetics
- AT TV — Intro to Pharmacology
- TV — Pharmacodynamics
- AT — Pharmacokinetics (PK): Chemical Properties
- TV — CSL: Knee Exam
- TV — CSL: Agenda Setting
- AT — Pharmacokinetics (PK): Parameters
- AT — Pharmacokinetics (PK): Analysis + Distribution
- AT — Pharmacokinetics (PK): Organ Clearance
- AT — Food & Drug Administration: FDA
- TV — Anatomy: Urinary, Endocrine, Reproductive
- AT — Pharmacokinetics (PK): Distribution
- TV — Drug Metabolism
- TV — Pharmacogenomics (PG)
- TV — Case study: PK, PD, PG

basic pharma principles

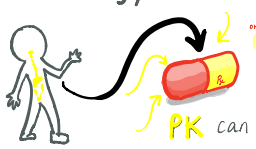
- ✓ DRUGS have both therapeutic actions and adverse reactions (ADRs)
- ✓ Before prescribing consider COST-BENEFIT analysis
- ✓ consider DRUG quality vs cost $ (high value care)
- ✓ ANTIBIOTIC STEWARDSHIP, multidrug resistant bacteria
- ✓ ALWAYS ask for-medication history
  - -vitamins, herbs, supplements
  - - medication allergies

PHARMACODYNAMICS vs PHARMACOKINETICS

ADME

PHARMACODYNAMICS: the effect that drugs have on the body

PHARMACOKINETICS: the study of how the body processes drugs in its system, in vivo



Most drugs...

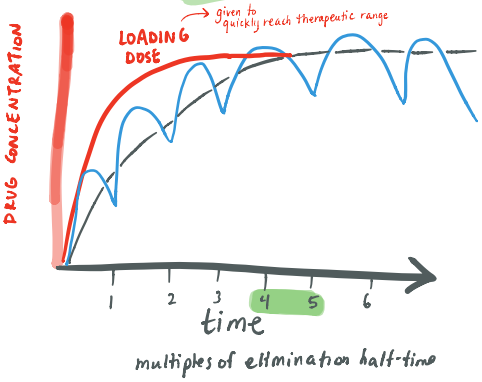
- ✓ chemically inert
- ✓ act @ low concentrations (potent)
- ✓ are saturable
- ✓ have activity that can be
  - stereoselectively changed structurally
  - inhibited by chemical analogs

Therapeutic Range

concentration that provides max benefit & minimum side effects

→ independent of dosage

STEADY STATE is achieved after 4 to 5 drug half-lives.

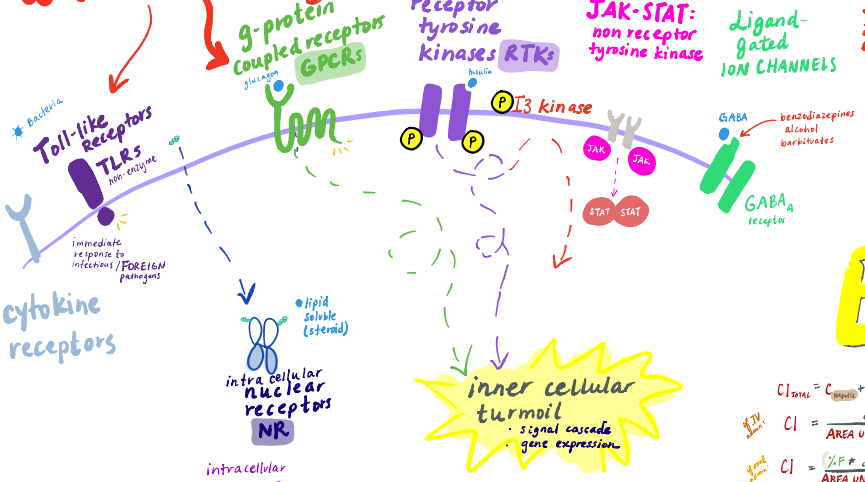


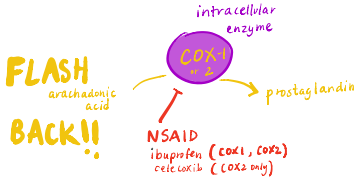
ALSO...

- ✓ time required to achieve higher C_p from dose increase = 4-5 half-lives
- ✓ time required for no detectable C_p after discontinuation of drug = 4-5 half-lives

where do drugs act?

ON RECEPTORS





EQUATIONS

! KNOW THESE & WHEN TO USE WHICH!

$Cl_{TOTAL} = C_{hepatic} + Cl_{Renal} + Cl_{other}$

$Cl = \frac{dose_{IV}}{AREA\ UNDER\ CURVE_{IV}}$

$Cl = \frac{\%F * dose_{oral}}{AREA\ UNDER\ CURVE_{oral}}$

$Cl_{organ} = Q * E$ (Q: organ blood flow; E: organ extraction ratio)

$V_d = \frac{drug\ in\ body}{C_p} = \frac{dose_{IV}}{C_0}$ (C_p: drug concentration in plasma/blood stream; C_0: extrapolation of drug concentration @ t=0)

$t_{1/2} = \frac{0.7}{K_{elim}} = 0.7 * \left(\frac{V_d}{Cl}\right)$

time to C_{ss} (steady state) = 4 * $t_{1/2}$

loading dose = target C_p × V_d

$R_0 = Cl * C_{ss}$ (steady state)

%F = bioavailability (→ fraction of drug that reaches circulation)

oral bioavailability = $\frac{AUC_{oral}}{AUC_{IV}} * \frac{dose_{IV}}{dose_{oral}} * 100$

DRUG·RECEPTOR Kinetics .... Michaelis Menten!

PARAMETER

velocity = $\frac{V_{max} \times [SUBSTR]}{K_m + [SUBSTR]}$ } substrate·enzyme

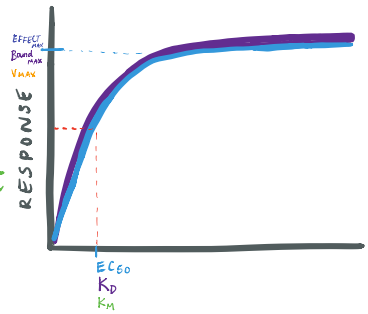
effect = $\frac{Effect_{MAX} \times [drug]}{EC_{50} + [drug]}$ } drug·receptor

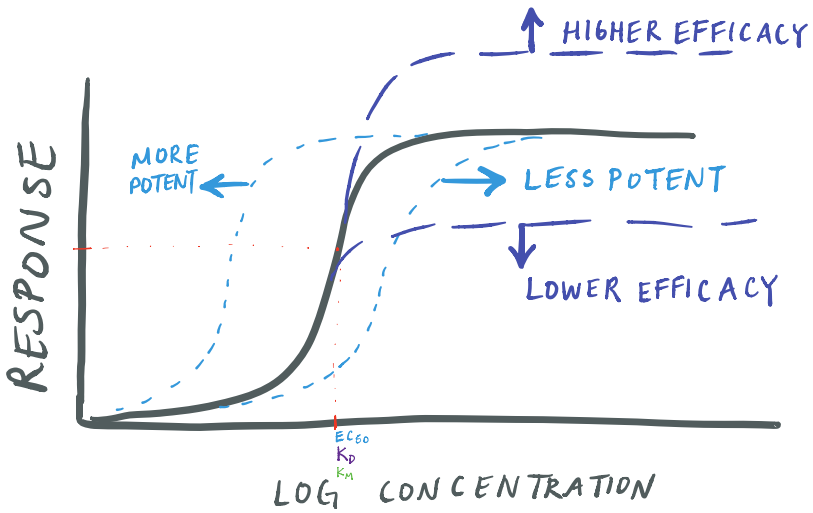
bound = $\frac{(Max\ Bound) \times [drug]}{K_D + [drug]}$

$E + S \rightleftharpoons ES \rightarrow E + P$

drug + R $\rightleftharpoons$ drug·R $\rightarrow$ effect

$K_D = \frac{k_{-1}}{k_1} = \frac{[drug][R]}{[drug{\cdot}R]}$





potency: AMOUNT of drug needed to produce an effect (EC_{50})

efficacy: drug's CAPACITY to produce an effected (E_{max})

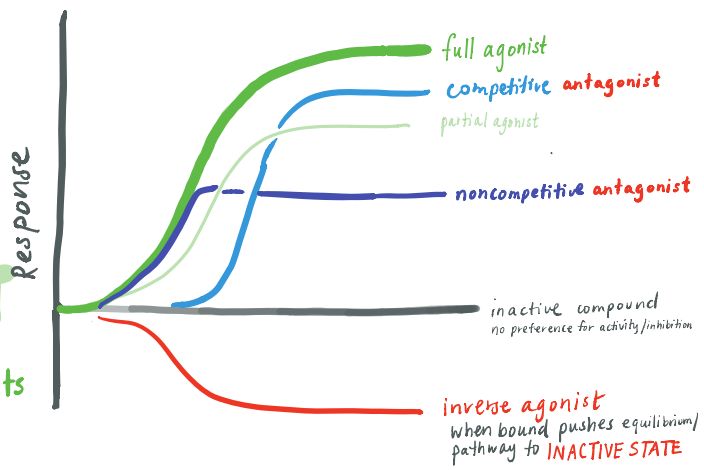
ANTAGONIST

COMPETITIVE ANTAGONIST

affects potency
shifts EC_{50} ↑
shifts curve RIGHT
eg NSAID, ibuprofen

NONCOMPETITIVE ANTAGONIST

affects efficacy
decreases E_{MAX}
shifts curve DOWN ↓
e.g. aspirin



PARTIAL AGONIST

binds fully but drug receptor binding yields LESS of a RESPONSE
effectively inhibits full agonists

MORE TERMINOLOGY

Desensitization

HOMOLOGOUS Desensitization
only signal from stimulated receptor is attenuated
e.g. specific covalent modification destruction/translocation of receptor

HETEROLOGOUS Desensitization
receptors that have diff. drug-binding interactions, but share common pathway are attenuated
pathway is desensitized (all doors lead to same hallway)

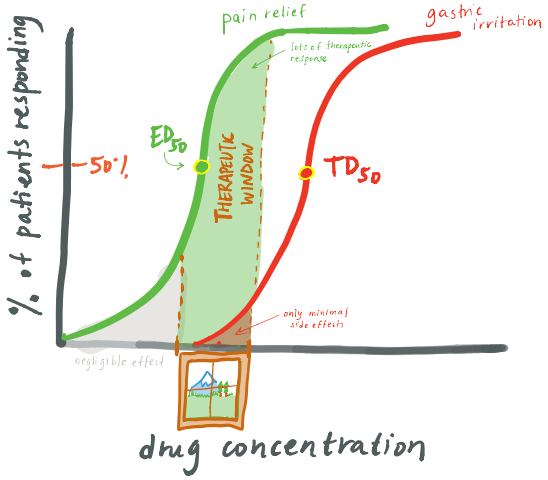
Chemical/Antagonism – one drug inhibits directly another drug, preventing its action

Biological/Physiological Antagonism – one drug working one one pathway COUNTERACTS the effects of another drug acting on a distinct pathway → neutral net effect
(binding to diff. receptors)

Therapeutic WINDOW

median effective dose
ED_{50} dose needed to produce effect in 50% of pop'n
TD_{50} dose needed to produce toxicity in 50% of pop'n
median toxic dose

$\frac{TD_{50}}{ED_{50}}$ = Therapeutic INDEX
indication of how selective a drug is in producing desired effects relative to undesired toxicity



SELECTIVE (most drugs)
- selectively prefers a given receptor, but exhibits activity @ >1 receptor site if concentration high enough

SPECIFIC
drug has one AND only effect on all biological systems

PHARMACOKINETICS

ADME

Routes of **INTRAVENOUS** vs **ORAL** administration

"I.V"

elimination through liver or kidneys
BBB (blood brain barrier) permeation of capillary epithelial barriers into target tissue/organ
plasma membrane permeation of target cell
exposure @ target

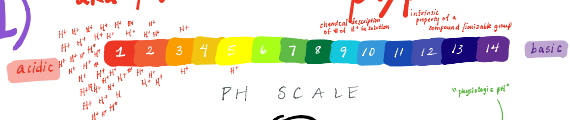
"p.o" "per os"

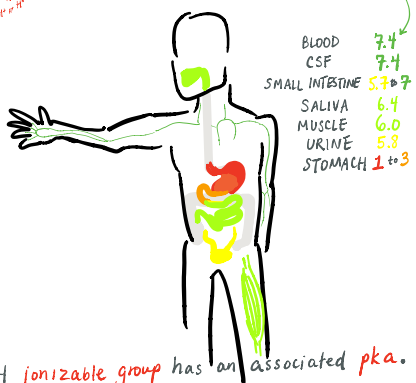
dissolution pH = 1.4 to 2.6
acidic pH of stomach, GI tract
GI metabolism
permeation of GI membrane into portal vein
first pass liver metabolism (PORTAL VEIN SYSTEM)
elimination through liver or kidneys
permeation of capillary epithelial barriers into target tissue/organ
plasma membrane permeation of target cell
exposure @ target

EACH STEP = BARRIER TO ACHIEVING FULL DRUG EXPOSURE

PHYSICOCHEMICAL properties of drugs

1) IONIZABLE FXNAL groups aka PHysiological relevance of pH/pka





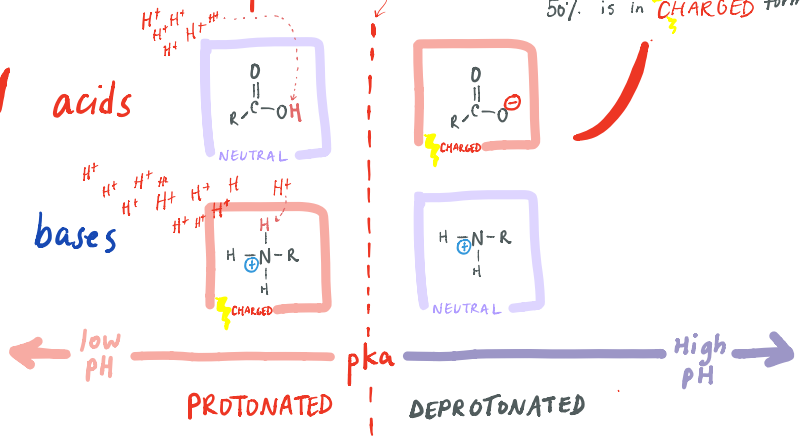
EACH ionizable group has an associated pka.

if the pH < pka, compound will most likely be in protonated form. and vice versa...

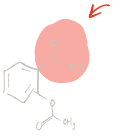
pka = the pH @ which 50% of drug exists in NEUTRAL form and 50% is in CHARGED form

CHARGED form = more plasma soluble can circulate around body more easily

NEUTRAL form = more membrane permeable can enter target cells more easily



Henderson-Hasselbach quantifies how much of each form exists @ a given pH



ionizable group
pka = 3.5

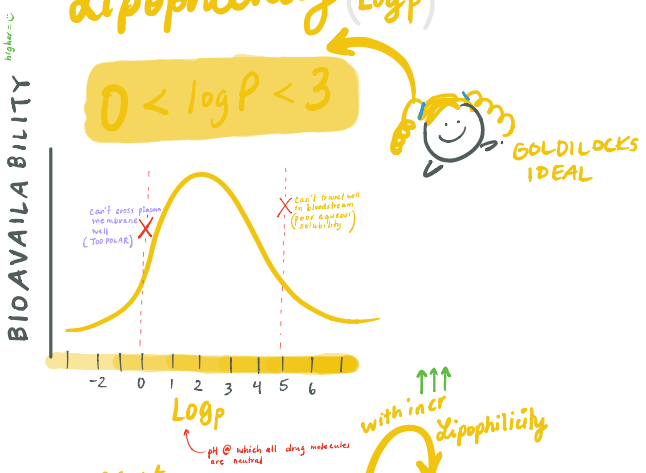
$pH = pka - \log \frac{[HA]^*}{[A^-]}$

stomach pH: $3.0 = 3.5 - \log \frac{[HA]}{[A^-]}$

$\frac{[HA]}{[A^-]}$ = 3 HA to 1 A^- ratio ⇒ Lower pH would allow neutral form of aspirin to predominate ↳ bigger therapeuti effect

* can cross membranes to provide therap effect

2) Lipophilicity (LogP)



Lipophilicity increases with

- ↑ incr # of C atoms
- ↓ # of polar fxnal groups (N, O – containing)
- ↑ # of rotatable bonds

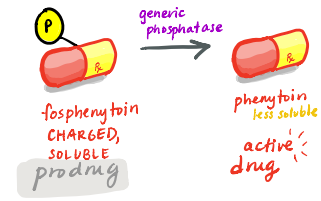
with incr Lipophilicity:

- ↑ volume of distribution
- ↑ speed of onset of axn
- ↓ duration of axn

e.g. propofol (brain anesthetic) has higher affinity for fat (high V_d) → distribution from brain → fat terminates its therapeutic effect

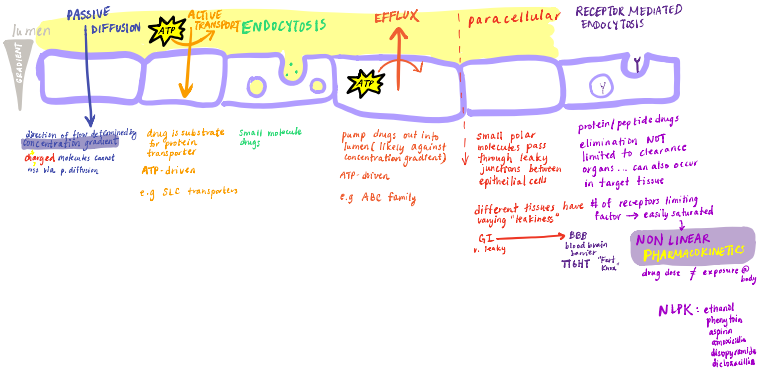
3) AQUEOUS SOLUBILITY

ex:



4) Membrane PERMEABILITY

↳ velocity (cm/s) of molecule passage thru membrane barrier



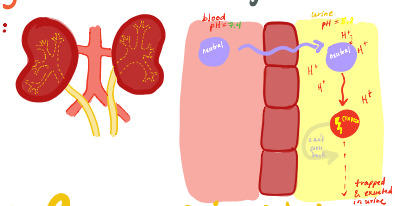
PK ADME

degree of distribution determined by:

+ ION TRAPPING in the kidney

if drug has pka at or near the pH gradient...
ion trapping can influence drug distribution in system.

ex:



TISSUE PERFUSION (blood flow)

- highly perfused TISSUES: kidneys, adrenals, thyroid, liver, heart, brain, lungs → fast drug distribution
- poorly perfused TISSUES: muscle, bone, skin, fat → slow drug distribution

PLASMA-BINDING proteins

- albumin (HSA)
- lipoproteins
- α1 glycoprotein

("carrier protein")

DRUG PROPERTY: acidic | neutral | basic

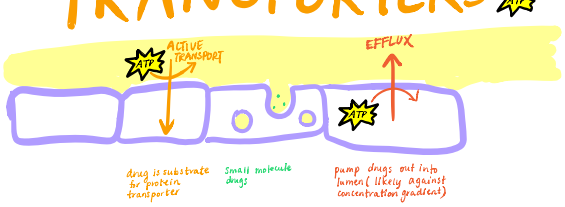
highly bound drug (large % of bound to albumin, e.g.) → limited effect on the body

- drug retained in plasma
- restricts V_d
- decr ↓ Cl and prolongs ↑ $t_{1/2}$
- limits BBB penetration

free drug (largely unbound) → larger effect on the body

- wider distribution, V_d
- therapeutic (+ adverse) effects
- ↑ incr Cl

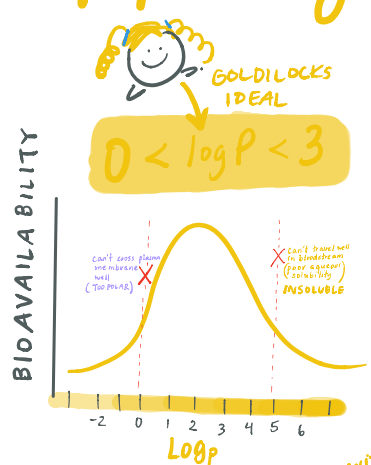
TRANSPORTERS



Solute carrier (SLC) transporters

ATP Binding Cassette transporters

Lipophilicity (LogP)



Lipophilicity increases with

- ↑ incr # of C atoms
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- ↑ # of rotatable bonds

with incr Lipophilicity:

- ↑ volume of distribution
- ↑ speed of onset of axn
- ↓ duration of axn

e.g. propofol

intrinsic values d/t chemical structure

VOLUME OF DISTRIBUTION

- indicates how widely the drug is distributed in the body
- proportionality of [drug] in plasma to total [drug] in body
- expressed in volume units: $\frac{L}{kg}$ $\frac{L}{70\,kg}$ $\frac{mL}{kg}$

0.07 — Confined to blood — e.g. warfarin

0.7 — evenly distributed — e.g. atenolol

7 (V_d High) — Highly bound in tissue — e.g. digoxin

? if a drug has Cl_H of 45 L/h and blood flow of 90 L/h, how much of drug is extracted by the liver in one pass?

half life $t_{1/2}$

the time it takes for a drug in systemic circulation to reduce by half → this value influenced by V_d and Cl

$$t_{1/2} = \frac{0.7}{K_{elim}} = 0.7 * \left(\frac{V_d}{Cl}\right)$$

larger $t_{1/2}$ value → drug has long half life, stays in body longer (associated w/ increasing V_d)

Log plot is linear for 1st order elimination process

? ∈ Rapidly eliminating drugs have → high? → clearance; low?

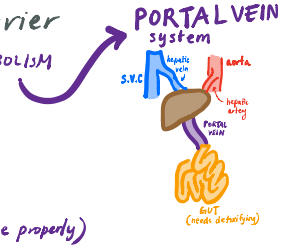
and/or → high? low? → vol. of distrib.

%F BIOAVAILABILITY

percentage of drug that reaches systemic circulation unchanged structurally, compared same dose given I.V.

all non-I.V routes involve an absorption barrier

	FIRST PASS METABOLISM
intramuscular	no
subcutaneous (sub-q)	no
inhaled	no
transdermal	no
sublingual/buccal	no (if done properly)
rectal	1st pass (not completely)
oral	1st pass (completely!)



EQUATIONS

$Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{other}$

IV: $Cl = \frac{dose_{IV}}{AREA\ UNDER\ CURVE_{IV}}$

Oral: $Cl = \frac{\%F * dose_{oral}}{AREA\ UNDER\ CURVE_{oral}}$

$Cl_{organ} = Q * E$ (Q: organ blood flow; E: organ extraction ratio)

$V_d = \frac{drug\ in\ body}{C_p} = \frac{dose_{IV}}{C_0}$ (C_p: drug concentration in plasma/blood stream; C_0: extrapolation of drug concentration @ t=0)

$t_{1/2} = \frac{0.7}{K_{elim}} = 0.7 * \left(\frac{V_d}{Cl}\right)$

time to C_{ss} = 4 * $t_{1/2}$ (steady state)

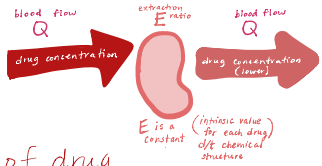
loading dose = target C_p * V_d

$R_0 = Cl * C_{ss}$ (steady state); R_0: infusion rate

%F = fraction of drug that reaches circulation; %F = bioavailability

oral bioavailability = $\frac{AUC_{oral}}{AUC_{IV}} * \frac{dose_{IV}}{dose_{oral}} * 100$

CLEARANCE



"volume of blood cleared of drug per unit time per body weight in kg"

describes the body's efficiency of elimination of a drug from systemic circulation

expressed in units of flow

L/hr/kg ml/min/kg

LIVER CLEARANCE

$Cl_H = Q_H * E_H$ determined by

- ✓ $f_{unbound}$ (f_u)
- ✓ intrinsic activity of drug-metab. enzymes (Cl_{int})
- ✓ liver blood flow ≈ (Q_H)

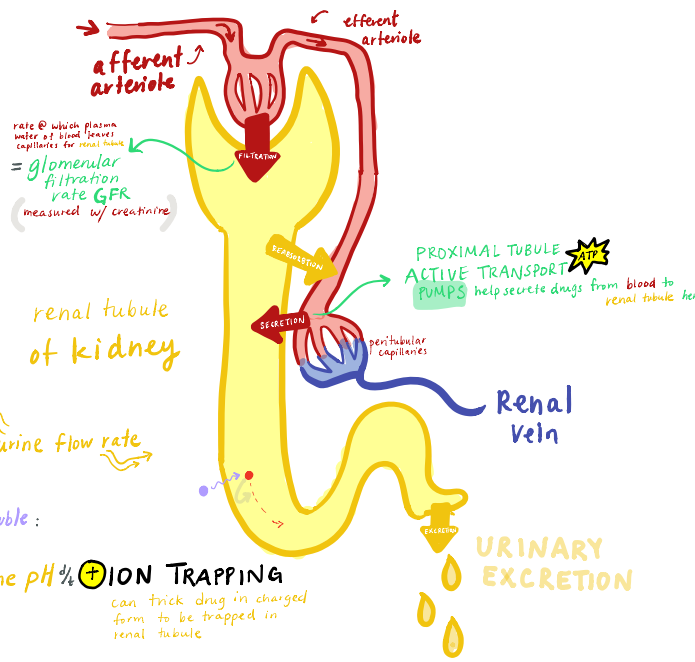
if E_H is low <0.3 → Cl_H determined by f_u (protein binding) & intrinsic enzyme activity

if E_H is high >0.7 → Cl_H determined by blood flow Q_H

RENAL CLEARANCE

Cl_R = filtration + secretion − reabsorption

$= f_u (GFR + Cl_{secretion})(1 - F_{reabsorbed})$



if drug is reabsorbable: Cl_R varies with urine flow rate

if drug is lipid-soluble + ionizable: Cl_R varies with urine pH % ION TRAPPING

can trick drug in charged form to be trapped in renal tubule

PK in CONTINUOUS & MULTIPLE DOSING SITUATIONS

A D M E

time to C_{pss} (steady state) = 4 * $t_{1/2}$

4-5 half-lives to reach steady C_{pss} STATE, accumulate drug eliminate drug

rate of drug input (infusion) = rate of drug output (elimination)

loading dose = target C_p × V_d

$R_0 = Cl * C_{pss}$ (steady state)

R_0 = infusion rate

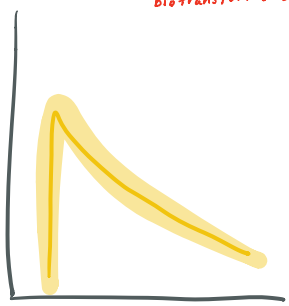
distribution ⇄ metabolism

distribution: plasma circulation, drug taken up by organs/tissues

metabolism: enzymes in tissues (liver) biotransforms drugs

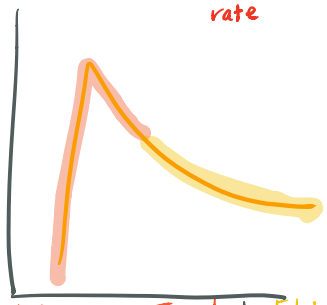
DISTRIBUTION ONLY

one compartment



ELIMINATION ONLY

one compartment



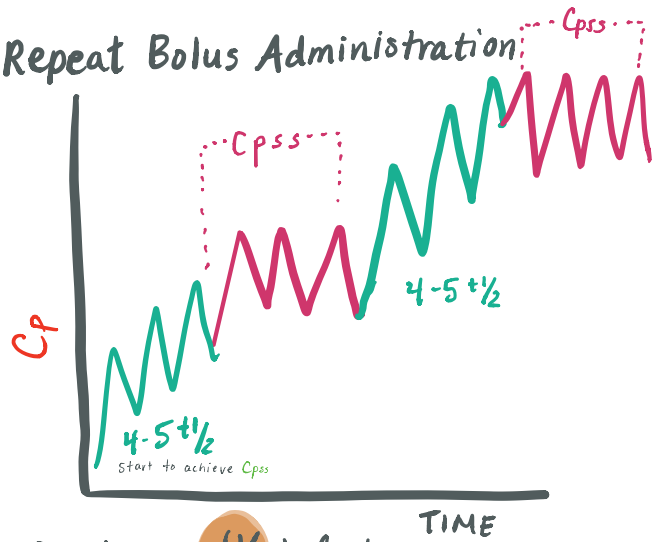
1st order kinetic elimination

DISTRIBUTION + ELIMINATION

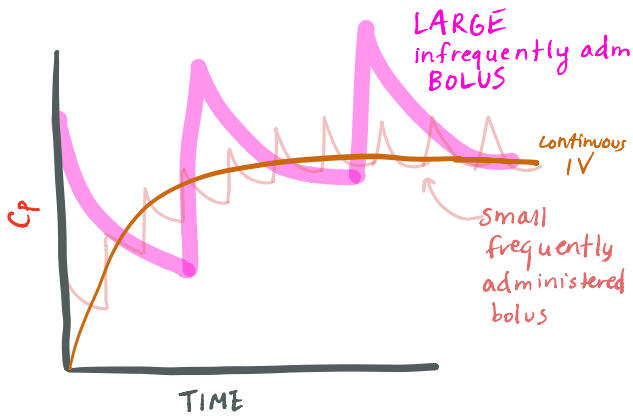
two compartments

drug moving from blood to tissue

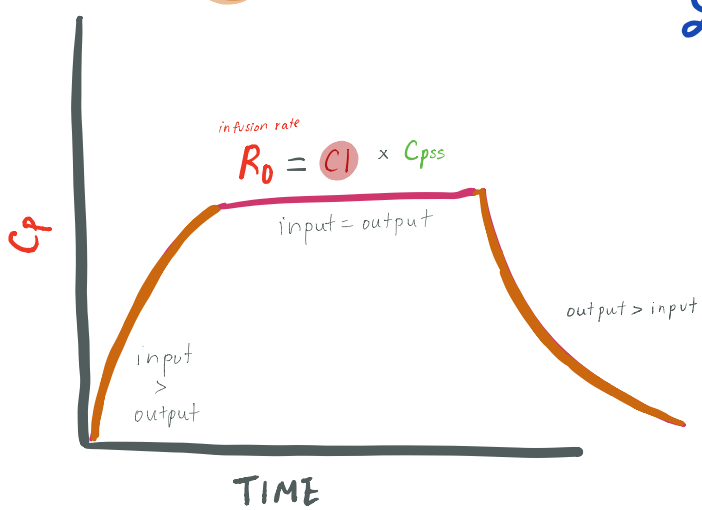
Repeat Bolus Administration



IV infusion vs Repeat Bolus



Continuous IV Infusion



Linear PK

all clinically used drugs = linear (predictable)

drug dose / drug exposure } linear relationship

→ AUC

NONLINEAR PK

UNDESIRABLE b.c. UNPREDICTABLE

drug dose / drug exposure ≠ linear relationship

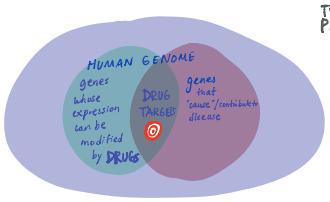
"capacity limited" "saturable" "dose limited"

"M-M elimin" "conc-dependent"

drugs w/ NONLINEAR PK: ethanol, phenytoin, aspirin, amoxicillin, disopyramide, dicloxacillin, biologics

only nonlinear @ high levels of drug (low levels = 1st order kinetics)

FDA Food & Drug ADMINISTRATION & DRUG DEVELOPMENT



TYPICAL PROPERTIES OF Successful drugs (Lipinski's RO5)

1. small (MW ≤ 500)
2. goldilocks lipophilic. ($\log P \leq 5$)
3. minimal H bonding capacity

nutraceuticals =
- supplements
- vitamins
- herbals

gray area of FDA regulation...
e.g. St. John's Wort

compound library screens "high throughput" leads are tweaked & developed to improve PK parameters

LONGEST STEP IN drug discovery

basic research → ! lead → preclinical development → (Investigational New Drug) IND filing → clinical development → (NEW Drug Application) NDA filing → FDA filing

DISCOVERY | DEVELOPMENT | APPROVAL | CLINICAL USE

in vitro → model animals (mice to rats to monkeys)

PHASE 1 → PHASE 2 → PHASE 3 → PHASE 4

PHASE 1: is it SAFE? pharmacokinetics, no severe toxicities; 10-100 healthy volunteers; 50% success rate

PHASE 2: does it work in PATIENTS? dose ranging; 50-500 patient-subjects; 30% success rate

PHASE 3: does it work on a larger scale, double blind? hundreds to thousands patient subjects; 25-50% success rate

PHASE 4: post marketing surveillance; many thousands patients in treatment w/ approved drug

generics become available 20 YEARS after patent filed (patent expires)

POPULATION GENETICS

	A	a
A	AA	Aa
a	Aa	aa

in HWE:

p = frequency of allele A

q = frequency of allele a

$$p^2 + 2pq + a^2 = 1$$

p^2: HOMOZYGOUS DOMINANT; $2pq$: HETEROZYGOUS; a^2: HOMOZYGOUS RECESSIVE

$$p + q = 1$$

HW equilibrium

"the genetic variation of a population will remain CONSTANT from one generation to the next in the absence of disturbing factors."

Hardy Weinberg law assumes:

1) NO mutation occurring @ locus
2) natural selection is not occurring
3) completely random mating
4) no net migration
5) large population

BIO- DRUG EQUIVALENCE

to be bioequivalent, AUC & Cmax must meet 80%-125% of brand name drug

GENERIC vs BRAND NAME

active ingredient (same) active ingredient = pharmaceutically equivalent ✓

different PK profile (not same) different PK profile = not therapeutically equivalent (always) ✗

+ EXCIPIENTS

everything in the pill besides active ingredient

- flavors
- pigment
- binders
- fillers

TRANSDERMAL DRUG delivery

lipophilic

"continuous infusion"-like

BIOLOGICS

proteins
peptides
monoclonal antibodies
DNA preps

} any drug made biologically

✓ susceptible to proteolytic degradation in GI (oral not good route)

✓ nonlinear PK if undergoing receptor-mediated endocytosis